is also more physiologically appropriate than previously described; subpiconewton forces are associated with RNA polymerase II transcription and with motor proteins within the nucleus (*4*).

Chromatin must undergo conformational changes during and after replication, as observed during mitosis, rearrangements during meiosis, and structural folding as the cell cycle progresses (*7*). Conformational changes are also observed during nuclear deformations, as observed when immune and cancer cells traverse distinct tissues (*8*). Local chromatin dynamics influence how transcription factors dock to target sequences and regulate long-range interactions between distant sequences (*7*). The observation that chromatin is fluid prompts reexamination of the biophysical principles underpinning these processes.

Two discoveries reported by Keizer *et al.* require the revisiting of existing ideas. That subpiconewton forces are sufficient to physically drag a locus within the genome across several micrometers in a crowded nucleus directly contradicts a previous finding that chromatin remains confined with submicrometer displacements after applications of larger forces (*4*). Possible explanations to reconcile these findings are the differences in the size of the probe and the amount of time that the forces were applied. Keizer *et al.* applied weaker forces for several minutes, whereas the previous experiment involved probes that were ~1000-fold larger and applied higher forces for 100-fold shorter time scales (*4*). Also, the labeling technique in the current study relies on the insertion of an artificial locus, whereas a native locus might reveal different flexibilities. Advances in CRISPR-mediated editing could be used to endogenously label chromatin to reconcile these findings.

The results reported by Keizer *et al.* also challenge the view that chromatin behaves as a stiff, cross-linked polymer gel (*3*–*6*). Polymers, including chromatin, are often depicted as linearized assemblies of individual units covalently linked in a Gaussian chain (*9*). These chains can be modeled as beads connected with harmonic springs. Instead, the authors observed that chromatin has fluidlike properties and behaves as a free polymer. The Rouse model is usually used for concentrated polymer solutions, where a drag force can be used to understand forces on the polymer as it undergoes motion with minimal contributions resulting from hydrodynamics (*9*). In the study of Keizer *et al.*, the observed dynamics suggested that there are moderate contributions of hindrance, topology, and cross-linking because of interactions with other chromatin regions in a crowded nucleus. One explanation might be that there may be subdomains within chromatin, where a mixture of states of gel-like domains are interspersed within the larger liquid structure. An additional explanation might be that the strength of the cross-linking is weak as a result of short-lived cross-links within the network of chromatin chains and associated factors. Thus, heterogeneity in the material properties might exist at different length scales. This may further clarify the differential transcriptional activities observed for the two forms of chromatin found within the nucleus (euchromatin and heterochromatin) (*1*, *2*).

Phase separation has been shown to drive the formation of heterochromatin domains (*10*). The dynamics of integrated loci that are fluidlike may also be important for phase separation of chromatin in vivo. Further studies involving the manipulation of additional chromosomes using endogenous probes will address the generalizability of the findings. The study of Keizer *et al.* also opens possibilities to mechanically manipulate gene loci in vivo. The authors cultured cells on pillars. However, mechanotransduction of longer-range forces, such as shear stress, differential tissue rigidity, or osmotic stresses, influence local chromatin dynamics through direct cross-talk between the nucleus and the extracellular milieu (*11*). Thus, coupling these technical advances with culture models, such as three-dimensional organoids, can be used to address the knowledge gap between micro- and mesoscale behaviors. ■

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ACKNOWLEDGMENTS

The authors are supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute.

10.1126/science.add5444

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CARBON NANOTUBES

Engineering defects with DNA

Single-walled carbon nanotubes are structurally modified by using a genetic sequence

By **YuHuang Wang**

Strategically introduced defects can be used to modify carbon nanotubes for new properties and functions. For example, chemical defects can act as atomic traps for electrons, holes, electron-hole pairs, and even molecules and ions (*1*). The ability to control the placement of these defects on carbon nanotubes could enable a plethora of fundamental studies and potential applications in imaging, sensing, disease diagnostics, and quantum information science (*2*–*4*). However, there is yet no effective way to do this with atomic precision (*5*–*7*). On page 535 of this issue, Lin *et al.* (*8*) report the creation of ordered defect arrays by programming DNA strands to wrap around and traverse the entire length of a single-walled carbon nanotube.

Modifications of single-walled carbon nanotubes are typically random, as all reactive sites on the extensive hexagonal lattice of the carbon nanotube are effectively the same (*7*). Lin *et al.* show that it is possible to program the placement of defects on the carbon lattice by using single-stranded DNA. In one example, they use a specific DNA strand made of guanine (G) and cytosine (C), with the sequence CCCGCCCCCCCGCCC, to wrap around a single-walled carbon nanotube, with each of the two guanines covalently linked to the nanotube forming an atomic defect (see the figure). The two defect sites are separated by five carbon-carbon bonds along a helical line of the hexagonal lattice known as the "armchair line," which travels down the nanotube similar to the threads on a screw. The process created ordered arrays of defects and pinned multiple DNA strands along the armchair line.

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Lin *et al.* observed this transformation using cryo–electron microscopy (cryo-EM), which measures the shadows of a macromolecule at many different orientations to reconstruct its three-dimensional (3D) structure. In their experiment, reconstructions from the cryo-EM images of 44,393 DNA-functionalized carbon nanotubes revealed that the single-stranded DNA forms a helical pitch of 6.5 Å, which closely matches the periodicity of the aforementioned armchair line of the carbon nanotube lattice. For comparison, this ordering is not observed in the controls. The formation of ordered defect arrays is also evidenced by spectral signatures that are strongly dependent on the spatial distribution pattern of the defects. When the two bonding G's are spaced at a distance that matches the helical pitch, the disorder-induced Raman scattering is minimized. Consistently, the defect photoluminescence peak shows minimum spectral shift and width at the same spacing between the G's and reveals a picture of populating electron-hole pairs, or excitons, between shallow defect traps in an array (*9*).

Although Lin *et al.* succeeded in designing a complex procedure for creating these defects, the exact mechanism behind the ordering remains somewhat of a mystery. The nanotubes are initially dispersed and stabilized individually in an aqueous solution by using a different DNA sequence (TTTCCCTTTCCCCCC; T is thymine), which is later displaced by bonding the G-containing sequence to the nanotube using 525-nm light to trigger the reaction. This guanine photochemistry creates covalent defects on single-walled carbon nanotubes, but the ordering of those defects was not previously observed (*6*). For these covalent defects to occur in an ordered array, the bonding reactions must occur in a way that avoids locking into a disordered configuration. To this end, the use of a water-methanol solvent might have allowed the defects to be created, as the methanol unwraps the dispersing DNA from the nanotube, making space for the reaction. Further research will be needed to decipher the mechanism of the ordering, which is important for designing and guiding the synthesis of these defect arrays.

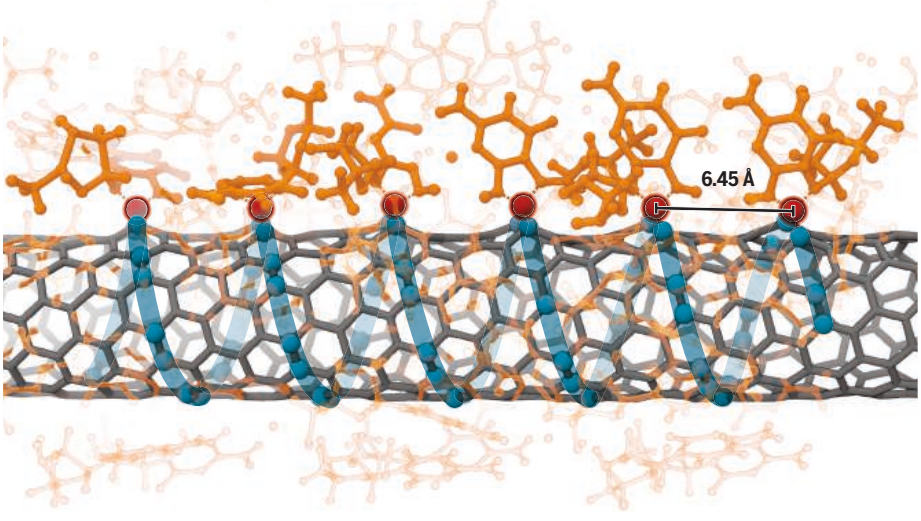
It is also worth highlighting the successful use of cryo-EM for resolving the oligonucleotides. Although cryo-EM has been powerful in determining the structure of proteins and other large biomolecules in the past, smaller molecules have typically been challenging for cryo-EM to resolve because of the low signal-to-noise ratio. The success here may be attributed, at least in part, to the nanotubes serving as an atomically precise ruler and reference for the 3D reconstruction. This "hack" may provide an exploit if it can be applied to resolving other small molecules that possess this property.

With a reliable method to create an ordered array of carbon nanotube defects, researchers may explore its applications—e.g., engineering defects as quantum traps to harness electron spins, excitons, trions, and single photons for a wide range of applications, such as in quantum chemical sensing (*1*). These traps, known as "sp^2" defects, are considerably shallower, and thus dimmer in photoluminescence, than "sp^3" defects, in which each carbon atom at the defect site is bonded to four instead of three other atoms (*10*). Although the weaker defect photoluminescence may limit the applications of these defects in areas such as imaging (*2*) and quantum light sources (*3*), their transport properties may be especially useful for a different assortment of applications. One such opportunity is for the experimental verification of the model for organic superconductors proposed more than 50 years ago by physicist Bill Little (*11*), in which he postulated that a room-temperature superconductor can be realized in a wire functionalized by ordered arrays of polarizable side chains that attract electrons. The finding by Lin *et al.* may provide a way to synthesize the wire imagined by Little and put the prediction to the test. The ability to program these defects along the length of a nanotube may also help create the so-called "Heisenberg spin chain," which can theoretically function as a chain of entangled quantum bits, with potential applications in quantum information processing and computing (*12*).

To realize these ambitious visions, future research efforts must expand and capitalize on the vast design space of DNAs, defect chemistry (*1, 13*), and precision nanotubes (*14*); enable deeper traps (*10*); and increase the size of the defect array. With the defect ordering demonstrated in this work, Lin *et al.*'s discovery (*8*) marks an important step, and the rush to order has started for defects. ■

Programming atomic defects on a carbon nanotube

By incorporating reactive guanines into a DNA sequence (orange), Lin *et al*. create ordered arrays of defects (red) at a pitch of ~6.5 Å along a helical line (blue) on the hexagonal lattice of a carbon nanotube (gray).



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ACKNOWLEDGMENTS

This work was partially supported by the National Science Foundation (grant nos. CHE2204202 and CHE1904488). I thank L. J. Wang for helping build the molecular model.

10.1126/science.abq2580

Engineering defects with DNA

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Science, **377** (6605), .
DOI: 10.1126/science.abq2580